WHAT IS CLAIMED IS:

General tiling claims

1. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least two sets of oligonucleotide probes,

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least three nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence,

(2) a second probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe in the second probe set being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the two corresponding probes from the first and second probe sets;

wherein the probes in the first probe set have at least two interrogation positions respectively corresponding to each of two contiguous nucleotides in the reference sequence.

2. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least four sets of oligonucleotide probes,

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least three nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence,

(2) second, third and fourth probe sets, each comprising a corresponding probe for each probe in the first probe set, the probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence

of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets.

3. The oligonucleotide array of claim 2, further comprising a fifth probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe from the fifth probe set being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is deleted in the corresponding probe from the fifth probe set.

4. The oligonucleotide array of claim 2, further comprising a sixth probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe from the sixth probe set being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that an additional nucleotide is inserted adjacent to the at least one interrogation position in the corresponding probe from the first probe set.

5. The array of claim 2, wherein the first probe set has at least three interrogation positions respectively corresponding to each of three contiguous nucleotides in a reference sequence.

6. The array of claim 2, wherein the first probe set has at least 50 interrogation positions respectively corresponding to each of 50 contiguous nucleotides in a reference sequence.

7. The array of claim 1 or 2, wherein the first probe set has at least 100 interrogation positions respectively

corresponding to each of 100 contiguous nucleotides in a reference sequence.

8. The oligonucleotide array of claim 1 or 2, wherein the first probe set has an interrogation position corresponding to each of at least 30% of the nucleotides in a reference sequence and the reference sequence comprises at least 100 nucleotides.

9. The oligonucleotide array of claim 8, wherein the first probe set comprises probes which completely span the reference sequence, which probes relative to the reference sequence, overlap one another in sequence.

10. The oligonucleotide array of claim 9, wherein the first probe set has an interrogation position corresponding to each of the nucleotides in the reference sequence.

11. The oligonucleotide array of claim 10, wherein the probes are oligodeoxyribonucleotides.

12. The oligonucleotide array of claim 1 or 2, wherein the array comprises between 100 and 10,000 probes.

13. The oligonucleotide array of claim 1 or 2, wherein the array comprises between 10,000 and 100,000 probes.

14. The oligonucleotide array of claim 1 or 2, wherein the array comprises between 100,000 and 10,000,000 probes.

15. The oligonucleotide array of claim 1 or 2, wherein the probes are linked to the support via a spacer.

16. The oligonucleotide array of claim 1 or 2, wherein the segment in each probe of the first probe set that is exactly complementary to the subsequence of the reference sequence is 9-21 nucleotides.

17. The oligonucleotide array of claim 16, wherein the segment is n nucleotides long, and the subsequence is at least n-2 nucleotides long.

18. The oligonucleotide array of claim 1 or 2, wherein each probe of the first probe set consists of the segment that is exactly complementary to the subsequence of the reference sequence.

19. The oligonucleotide array of claim 1 or 2, wherein the probes in the second, third and fourth probe sets are identical to the corresponding probe from the first probe set except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets.

20. The array of claim 2, further comprising fifth, sixth and seventh probe sets, wherein:

the segment of each probe in the first set includes at least two interrogation positions each corresponding to a nucleotide in the reference sequence,

the second, third and fourth probe sets, each comprise a corresponding probe for each probe in the first probe set, the corresponding probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes a first interrogation position except that the first interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets;

the fifth, sixth and seventh probe sets, each comprising a corresponding probe for each probe in the first probe set, the probes in the fifth, sixth and seventh probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes a second interrogation position, except that the second interrogation

position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets.

21. The array of claim 2, wherein each probe in the first probe set further comprises a second segment of at least three nucleotides exactly complementary to a second subsequence of the reference sequence, and the probes from the second, third and fourth probe sets comprise the corresponding probe from the first probe set or a subsequence thereof comprising the first and second segments except in the at least one interrogation position.

22. The array of claim 2, further comprising:

a fifth probe set comprising at least one probe comprising a segment of at least seven nucleotides exactly complementary to a subsequence of the reference sequence except at one or two positions, the segment including at least one interrogation position corresponding to a nucleotide in the reference sequence not at the one or two positions;

sixth, seventh and eighth probe sets, each comprising a probe for each probe in the fifth probe set, the corresponding probes from the sixth, seventh & eighth probe sets being identical to a sequence comprising the corresponding probe from the fifth probe set or a subsequence of at least nine nucleotides thereof including the at least one interrogation position and the one or two positions, except in the at least one interrogation position, which is occupied by a different nucleotide in each of the four probes.

23. The array of claim 2, wherein the probes are arranged on the substrate so that the first set of probes is arranged in a row across the substrate in an order reflecting the overlap between the probes and the reference sequence, and the additional sets of probes are arranged in columns relative to the probes in said first set, so that probes with the same interrogation position are in the same column and so that each column comprises at least 4 probes.

24. The array of Claim 2, wherein said probes are 12 to 17 nucleotides in length.

25. The array of Claim 2, wherein said probes are 15 nucleotides in length and attached by a covalent linkage to a site on a 3'-end of said probes, and said interrogation position is located at position 7, relative to the 3'-end of said probes.

26. The array of claim 2, further comprises fifth, sixth, seventh and eighth probe sets,

(1) a fifth probe set comprising a plurality of probes, each probe comprising a segment of at least three nucleotides exactly complementary to a subsequence of a second reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence,

(2) the sixth, seventh, and eighth probe sets, each comprising a corresponding probe for each probe in the fifth probe set, the probes in the sixth, seventh and eighth probe sets being identical to a sequence comprising the corresponding probe from the fifth probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the fifth, sixth, seventh and eighth probe sets.

27. The array of claim 22, wherein the first, second, third and fourth probe sets have probes of a first length and the fifth, sixth, seventh and eight probe sets have probes of a second length different from the first length.

Tiling for wildtype and mutant reference sequences

28. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least one pair of first and second probe groups, each group comprising a first and second sets of oligonucleotide probes as defined by claim 1;

wherein each probe in the first probe set from the first group is exactly complementary to a subsequence of a first reference sequence and each probe in the first probe set from the second group is exactly complementary to a subsequence from a second reference sequence.

29. The array of claim 28, wherein the second reference sequence is a mutated form of the first reference sequence.

30. The array of claim 28, wherein each group further comprises third and fourth probe sets, each comprising a corresponding probe for each probe in the first probe set, the probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the interrogation position, except that the interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets.

31. The array of claim 30 that comprises at least five pairs of first and second probe groups, wherein the probes in the first probe sets from the first groups of the five pairs are exactly complementary to subsequences from five different respective first reference sequences.

32. The array of claim 30 that comprises at least forty pairs of first and second probe groups, wherein the probes in the first probe sets from the first groups of the forty pairs are exactly complementary to subsequences from forty respective first reference sequences.

Block tiling

33. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least a group of probes comprising:

a wildtype probe comprising a segment of at least three nucleotides exactly complementary to a subsequence of a

reference sequence, the segment having at least first and second interrogation positions corresponding to first and second nucleotides in the reference sequence,

a first set of three mutant probes, each identical to a sequence comprising the wildtype probe or a subsequence of at least three nucleotides thereof including the first and second interrogation positions, except in the first interrogation position, which is occupied by a different nucleotide in each of the three mutant probes and the wildtype probe;

a second set of three mutant probes, each identical to a sequence comprising the wildtype probe or a subsequence of at least three nucleotides thereof including the first and second interrogation positions, except in the second interrogation position, which is occupied by a different nucleotide in each of the three mutant probes and the wildtype probe.

34. The array of claim 33, wherein the segment of the wildtype probe comprises 3-20 interrogation positions corresponding to 3-20 respective nucleotides in the reference sequence, and the array comprises 3-20 respective sets of three mutant probes, each of the three probes identical to a sequence comprising the wildtype probe or a subsequence thereof including the 3-20 interrogation positions, except that one of the 3-20 interrogation positions is occupied by a different nucleotide in each of the three mutant probes and the wildtype probes, the one of the 3-20 interrogation positions being different in each of the 3-20 respective sets of three mutant probes.

35. An array of probes immobilized to a solid support comprising two groups of probes, each group as defined by claim 33, a first group comprising a wildtype probe comprising a segment exactly complementary to a subsequence of a first reference sequence and a second group comprising a wildtype probe comprising a segment exactly complementary to a subsequence of a second reference sequence.

36. The array of claim 35, comprising at least 10-100 groups of probes, each comprising a wildtype probe comprising a segment exactly complementary to a subsequence of at least 10-100 respective reference sequences.

Pooled probes

37. A method of comparing a target sequence with a reference sequence, the method comprising:

identifying variants of a reference sequence differing from the reference sequence in at least one nucleotide;

assigning each variant a designation,

providing an array of pools of probes, each pool occupying a separate cell of the array, wherein each pool comprises a probe comprising a segment exactly complementary to each variant sequence assigned a particular designation,

contacting the array with a target sequence comprising a variant of the reference sequence;

determining the relative hybridization intensities of the pools in the array to the target sequence;

determining the target sequence from the relative hybridization intensities of the pools.

38. The method of claim 37, wherein the variants are assigned numbers according to an error code.

39. The method of claim 37, wherein each variant is assigned a designation having at least one digit and at least one value for the digit, and each pool comprise a probe comprising a segment exactly complementary to each variant sequence assigned a particular value in a particular digit.

40. The method of claim 39, wherein the variants are assigned successive numbers in a numbering system of base m having n digits, and the array comprises n x (m-1) pools of probes.

41. The method of claim 40, wherein each pool further comprises a probe comprising a segment exactly complementary to the reference sequence.

Trellis tiling

42. A pooled probe comprising a segment exactly complementary to a subsequence of a reference sequence except at a first interrogation position occupied by a pooled nucleotide N, a second interrogation position occupied by a pooled nucleotide selected from the group of three consisting of (1) M or K, (2) R or Y and (3) S or W, and a third interrogation position occupied by a second pooled nucleotide selected from the group, wherein the pooled nucleotide occupying the second interrogation position comprises a nucleotide complementary to a corresponding nucleotide from the reference sequence when the second pooled probe and reference sequence are maximally aligned, and the pooled nucleotide occupying the third interrogation position comprises a nucleotide complementary to a corresponding nucleotide from the reference sequence when the third pooled probe and the reference sequence are maximally aligned, wherein N is A, C, G or T(U), K is G or T(U), M is A or C, R is A or G, Y is C or T(U), W is A or T(U) and S is G or C.

43. An array of oligonucleotide probes immobilized on solid support, the array comprising:

first, second and third cells respectively occupied by first, second and third pooled probes, each pooled probe comprising a segment exactly complementary to a subsequence of a reference sequence except at a first interrogation position occupied by a pooled nucleotide N, a second interrogation position occupied by a pooled nucleotide selected from the group of three consisting of (1) M or K, (2) R or Y and (3) S or W, and a third interrogation position occupied by a second pooled nucleotide selected from the group, wherein the pooled nucleotide occupying the second interrogation position comprises a nucleotide complementary to a corresponding nucleotide from the reference sequence when the pooled probe

and the reference sequence are maximally aligned, and the pooled nucleotide occupying the third interrogation position comprises a nucleotide complementary to a corresponding nucleotide from the reference sequence when the pooled probe and the reference sequence are maximally aligned;

provided that one of the three interrogation positions in the each of the three pooled probes is aligned with the same corresponding nucleotide in the reference sequence, this interrogation position being occupied by an N in one of the pooled probes, and a different pooled nucleotide in each of the other two pooled probes,

wherein N is A, C, G or T(U), K is G or T(U), M is A or C, R is A or G, Y is C or T(U), W is A or T(U) and S is G or C.

44. The array of claim 43 further comprising:

fourth and fifth cells respectively occupied by fourth and fifth pooled probes, each pooled probe as defined by claim 43,

wherein one of the three interrogation position in the second, third and fourth pooled probes is aligned with the same corresponding nucleotide in the reference sequence, this interrogation position being occupied by an N in one of the pooled probes, and a different pooled nucleotide in each of the other two pooled probes,

wherein one of the three interrogation position in the third, fourth and fifth pooled probes is aligned with the same corresponding nucleotide in the reference sequence, this interrogation position being occupied by an N in one of the pooled probes, and a different pooled nucleotide in each of the other two pooled probes.

45. The array of claim 44, wherein the pooled probes are identical except at the interrogation positions.

46. The array of claim 44, wherein the first, second, third, fourth and fifth pooled probes are exactly complementary to five respective subsequences of the reference

sequences that from each other by increments of one nucleotide.

Bridge tiling

47. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least four probes:

a first probe comprising first and second segments, each of at least three nucleotides and exactly complementary to first and second subsequences of a reference sequences, the segments including at least one interrogation position corresponding to a nucleotide in the reference sequence, wherein either (1) the first and second subsequences are noncontiguous, or (2) the first and second subsequences are contiguous and the first and second segments are inverted relative to the complement of the first and second subsequences in the reference sequence;

second, third and fourth probes, identical to a sequence comprising the first probe or a subsequence thereof comprising at least three nucleotides from each of the first and second segments, except in the at least one interrogation position, which differs in each of the probes.

48. The array of claim 47, wherein the first and second subsequences are separated by one or two nucleotides in the reference sequence.

Two interrogation positions (no wildtype)

49. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least a set of four probes, each of the probes comprising a segment of at least 7 nucleotides that is exactly complementary to a subsequence from a reference sequence, except that the segment may or may not be exactly complementary at two interrogation positions, wherein:

the first interrogation position is occupied by a different nucleotide in each of the four probes,

the second interrogation position is occupied by a different nucleotide in each of the four probes,

in first and second probes, the segment is exactly complementary to the subsequence, except at not more than one of the interrogation positions, and

in third and fourth probes, the segment is exactly complementary to the subsequence, except at both of the interrogation positions.

50. An array of probes immobilized to a support, the array comprising at least 100 sets of 4 probes, each set as defined by claim 49, the probes from the at least 100 sets comprising at least 100 respective segments, the segments having at least 100 respective first and second interrogation positions.

Helper mutations

51. An array of oligonucleotide probes immobilized on a solid support, the array comprising a set of probes comprising:

a first probe comprising a segment of at least 7 nucleotides exactly complementary to a subsequence of a reference sequence except at one or two positions, the segment including an interrogation position not at the one or two positions;

second, third and fourth mutant probes, each identical to a sequence comprising the wildtype probe or a subsequence thereof including the interrogation position and the one or two positions, except in the interrogation position, which is occupied by a different nucleotide in each of the four probes.

Omission of Perfectly Matched Probe

52. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least two sets of oligonucleotide probes,

(1) a first probe set comprising a plurality of probes, each probe comprising a segment exactly complementary to a subsequence of at least 3 nucleotides of a reference sequence except at an interrogation position,

(2) a second probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe in the second probe set being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the interrogation position, except that the interrogation position is occupied by a different nucleotide in each of the two corresponding probes and the complement to the reference sequence,

wherein the probes in the first probe set have at least three interrogation positions respectively corresponding to each of three contiguous nucleotides in the reference sequence.

Methods

53. A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing the target nucleic acid to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least three nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence,

(2) a second probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe in the second probe set being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the two corresponding probes from the first and second probe sets;

wherein, the probes in the first probe set have at least three interrogation positions respectively corresponding

to each of at least three nucleotides in the reference sequence, and

(b) determining which probes, relative to one another, in the array bind specifically to the target nucleic acid, the relative specific binding of the probes indicating whether the target sequence is the same or different from the reference sequence.

54. The method of claim 53, wherein the array further comprises third and fourth probe sets, each comprising a corresponding probe for each probe in the first probe set, the probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets.

55. The method of claim 54, wherein the target sequence has a substituted nucleotide relative to the reference sequence in at least one undetermined position, and the relative specific binding of the probes indicates the location of the position and the nucleotide occupying the position in the target sequence.

56. The method of claim 54, wherein:

the hybridizing step comprises hybridizing the target nucleic acid and a second target nucleic acid to the array; and

the determining step comprises determining which probes, relative to one another, in the array bind specifically to the target nucleic acid or the second target nucleic acid, the relative specific binding of the probes indicating whether the target sequence is the same or different from the reference sequence and whether the second

target sequence is the same or different from the reference sequence.

57. The method of claim 56, wherein the target sequence has a label and the second target sequence has a second label different from the label.

58. The method of claim 56, wherein undetermined first and second proportions of the first and second target sequences are hybridized to the array and the specific binding indicates the proportions.

59. The method of claim 54, further comprising:

(c) removing the target nucleic acid from the array;

(d) hybridizing a second target nucleic acid to the array;

(e) determining which probes, relative to one another, in the array bind specifically to the second target nucleic acid, the relative specific binding of the probes indicating whether the second target sequence is the same or different from the reference sequence.

60. A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

hybridizing the target sequence to the array of claim 28;

determining which probes in the first group, relative to one another, hybridize to the target sequence, the relative specific binding of the probes indicating whether the target sequence is the same or different from the first reference sequence;

determining which probes in the second group, relative to one another, hybridize to the target sequence, the relative specific binding of the probes indicating whether the target sequence is the same or different from the second reference sequence.

61. The method of claim 60, wherein the hybridizing step comprising hybridizing the target sequence and a second target sequence to the array, and the relative specific binding of the probes from the first group indicates that the target is identical to the first reference sequence, and the relative specific binding of the probes from the second group indicates that the second target sequence is identical to the second reference sequence.

62. The method of claim 61, wherein the first and second target sequences are heterozygous alleles of a gene.

Comparative hybridization

63. A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing the reference sequence to an array of oligonucleotide probes immobilized on a solid support, the array comprising;

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least 3 nucleotides exactly complementary to a subsequence of the reference sequence except in at least one interrogation position;

(2) a second probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe in the second probe set being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the two corresponding probes from the first and second probe sets; and

(b) determining which probes, relative to one another, in the array bind specifically to the reference sequence;

(c) hybridizing a target sequence to the array;

(d) determining which probes, relative to one another, in the array bind specifically to the target sequence;

wherein the relative specific binding of the probes to the reference and the target sequence indicates whether the reference sequence is the same or different from the target sequence.

64. The method of claim 63, wherein the reference sequence has a first label and the second reference sequence has a second label different from the first label, and steps (a) and (c) are performed simultaneously.

HIV Chip

65. The array of claim 2, wherein the reference sequence is from a human immunodeficiency virus.

66. The array of claim 65, wherein the reference sequence is from a reverse transcriptase gene of the human immunodeficiency virus.

67. The array of claim 66, wherein the reference sequence is from a protease gene of the human immunodeficiency virus.

68. The array of claim 66, wherein the reference sequence is a full-length reverse transcriptase gene.

69. The array of claim 68 comprising at least 3200 oligonucleotide probes.

70. The array of claim 66, wherein the HIV gene is from the BRU HIV strain.

71. The array of claim 66, wherein the HIV gene is from the SF2 HIV strain.

72. The array of claim 28, wherein the reference sequence is from the coding strand of a reverse transcriptase gene of a human immunodeficiency virus and the second reference sequence is from the noncoding strand of the reverse transcriptase gene.

73. The array of claim 28, wherein the first reference sequence is from a reverse transcriptase gene of a human immunodeficiency virus and the second reference sequence comprises a subsequence of the first reference sequence with a substitution of at least one nucleotide.

74. The array of claim 73, wherein the substitution confers drug resistance to a human immunodeficiency virus comprising the second reference sequence.

75. The array of claim 28, wherein the first and second reference sequences are from a reverse transcriptase gene from first and second strains of a human immunodeficiency virus.

76. The array of claim 28, wherein the first reference sequence is from a reverse transcriptase gene of a human immunodeficiency virus and the second reference sequence is from a 16S RNA, or DNA encoding the 16S RNA, from a pathogenic microorganism.

77. The array of claim 28, wherein the first reference sequence is from a reverse transcriptase gene of a human immunodeficiency virus and the second reference sequence is from a protease gene of the human immunodeficiency virus.

78. The method of claim 54, wherein the reference sequence is from a human immunodeficiency virus.

79. The method of claim 78, wherein the reference sequence is from a human immunodeficiency virus and the target sequence is from a second human immunodeficiency virus.

80. The method of claim 79, wherein the target sequence has a substituted nucleotide relative to the reference sequence in at least one undetermined position, and the relative specific binding of the probes indicates the location of the position and the nucleotide occupying the position in the target sequence.

81. The method of claim 80, wherein the target sequence has a substituted nucleotide relative to the reference sequence in at least one position, the substitution conferring drug resistance to the human immunodeficiency virus, and the relative specific binding of the probes reveals the substitution.

82. The method of claim 78, wherein:

the hybridizing step comprises hybridizing the target nucleic acid and a second target nucleic acid, the second target sequence being from a reverse transcriptase gene of a third human immunodeficiency virus, to the array; and

the determining step comprises determining which probes, relative to one another, in the array bind specifically to the target nucleic acid or the second target nucleic acid, the relative specific binding of the probes indicating whether the target sequence is the same or different from the reference sequence and whether the second target sequence is the same or different from the reference sequence.

83. The method of claim 82, wherein the first target sequence has a first label and the second target sequence has a second label different from the first label.

84. The method of claim 82, wherein undetermined first and second proportions of the first and second target sequences are hybridized to the array and the specific binding indicates the proportions.

CFTR Chip

85. The array of claim 2, wherein the reference sequence is from a CFTR gene.

86. The array of claim 85, wherein the reference sequence is exon 10 of a CFTR gene, and said array comprises over 1000 oligonucleotide probes, 10 to 18 nucleotides in length.

87. The array of claim 85, wherein said array comprises a set of probes comprising a specific nucleotide sequence selected from the group of sequences comprising:
3'-TTTATAXTAG;
3'- TTATAGXAGA;
3'- TATAGTXGAA;
3'- ATAGTAXAAA;
3'- TAGTAGXAAC;
3'- AGTAGAXACC;
3'- GTAGAAXCCA;
3'- TAGAAAXCAC; and
3'- AGAAACXACA; wherein each set comprises 4 probes, and X is individually A, G, C, and T for each set.

88. The array of claim 85, wherein said group of sequences comprises:
3'-TTTATAXTAGAAACC;
3'- TTATAGXAGAAACCA;
3'- TATAGTXGAAACCAC;
3'- ATAGTAXAAACCACA;
3'- TAGTAGXAACCACAA;
3'- AGTAGAXACCACAAA;
3'- GTAGAAXCCACAAAG;
3'- TAGAAAXCACAAAGG; and
3'- AGAAACXACAAAGGA; wherein each set comprises 4 probes, and X is individually A, G, C, and T for each set.

89. The array of claim 32, wherein the forty first reference sequences are from a CFTR gene.

90. The array of claim 89, wherein each of the forty first reference sequences includes a site of a mutation and at least one adjacent nucleotide.

91. The array of claim 90, wherein each of the forty first reference sequences comprises at least five contiguous nucleotides from a CFTR gene.

92. The array of claim 89, wherein at least one first reference sequence is a from the coding strand of the cystic fibrosis gene and at least one first reference sequence is from the noncoding strand of the CFTR gene.

93. An array of oligonucleotide probes immobilized on a solid support, the array comprising at least a group of probes comprising:

a wildtype probe exactly complementary to a subsequence of a reference sequence from a cystic fibrosis gene, the segment having at least five interrogation positions corresponding to five contiguous nucleotides in the reference sequence,

a first set of three mutant probes, each identical to the wildtype probe, except in a first of the five interrogation positions, which is occupied by a different nucleotide in each of the three mutant probes and the wildtype probe;

a second set of three mutant probes, each identical to the wildtype probe, except in a second of the five interrogation positions, which is occupied by a different nucleotide in each of the three mutant probes and the wildtype probe;

a third set of three mutant probes, each identical to the wildtype probe, except in a third of the five interrogation positions, which is occupied by a different nucleotide in each of the three mutant probes and the wildtype probe;

a fourth set of three mutant probes, each identical to the wildtype probe, except in a fourth of the five interrogation positions, which is occupied by a different

nucleotide in each of the three mutant probes and the wildtype probe;

a fifth set of three mutant probes, each identical to the wildtype probe, except in a fifth of the five interrogation positions, which is occupied by a different nucleotide in each of the three mutant probes and the wildtype probe.

94. The array of claim 93 comprising first and second groups of probes, each group as defined by claim 93, the first group comprising a wildtype probe exactly complementary to a first reference sequence, and the second group comprising a wildtype probe exactly complementary to a second reference sequence, wherein the second reference sequence is a mutated form of the first reference sequence.

95. The array of claim 94, wherein the first reference sequence is from a CFTR gene and the second reference sequence is a mutated form of the first reference sequence.

96. The method of claim 56, wherein the target sequence and the second target sequence are from heterozygous alleles of a CFTR gene.

P53 Chip

97. The array of claim 2, wherein the reference sequence is a sequence from a p53 gene.

98. The array of claim 2, wherein the reference sequence is from an hMLH1 gene.

99. The array of claim 2, wherein the reference sequence is from an MSH2 gene.

100. The array of claim 28, wherein the reference sequence is from a human P53 gene and the second reference sequence is from an hMLH1 gene.

101. The array of claim 100, further comprising:

ninth, tenth, eleventh and twelfth probe sets,

(1) the ninth probe set comprising a plurality of probes, each probe comprising a segment of at least three nucleotides exactly complementary to a subsequence of a third reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the third reference sequence,

(2) the tenth, eleventh and twelfth probe sets, each comprising a corresponding probe for each probe in the ninth probe set, the probes in the tenth, eleventh and twelfth probe sets being identical to a sequence comprising the corresponding probe from the ninth probe set or a subsequence of at least three nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the ninth, tenth, eleventh and twelfth probe sets.

102. The array of claim 97, wherein the first probe set has at least 60 interrogation positions corresponding to at 60 contiguous nucleotides from exon 6.

103. The array of claim 98, wherein the reference sequence is exon 5 of a p53 gene, the probes are 17 nucleotides long, and the first set of probes is exactly complementary to the reference sequence, and the at least one interrogation position is at position 7, relative to a 3'-end of each probe, which 3'-end is covalently attached to the substrate.

Mitochondrial Chip

104. The array of claim 2, wherein the reference sequence is from a mitochondrial genome.

105. The array of claim 104, wherein said reference sequence is a sequence of a D-loop region.

106. The array of claim 105, wherein D-loop region is full-length.

107. The array of claim 104, wherein said reference sequence is at least 90% of a full-length mitochondrial genome.

108. The array of claim 104, wherein the reference sequence is bounded by positions 16280 to 356 of the mitochondrial genome.